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OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
SAKELARIS, SALLY A	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/926,028	MAEKAWA ET AL.	
	Examin r	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Final Rejection

This action is written in response to applicant's correspondence submitted June 25, 2003. Claims 1, 3-6, and 8 have been amended and claims 9-20 have been added. Claims 1-20 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Priority

Acknowledgement of claim to foreign priority of Japanese Application, 11/38538, filed 2/17/1999 under 35 U.S.C. 119(a)-(d) has been made, however applicant should note that the paper received 7/30/2002 consisting of 109 pages corresponds to PCT/JP00/00092 not PCT/JP00/00902 and as a result the claim to foreign priority under the same has not yet been granted.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The term " near the 5' end " in claim 1 is a relative term which renders the claim indefinite. The term " near the 5' end " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear if "near" is to mean within 5 nucleotides, 10 nucleotides, 100 nucleotides, etc. of the 5' end of the strand having the poly(T) sequence. Applicant should amend the claim to clarify their intended meaning and placement of the restriction enzyme site that is placed "near the 5' end".

B. The term " at a downstream position from the recognition sequence for the second restriction enzyme " in claim 1 is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what the reference point is for the instruction of "downstream position". A recognition sequence is had by both strands of the DNA sequence and as a result provides an indefinite placement of the position that is "downstream". Applicant must amend the claim to clarify at which end of which strand the type IIS restriction enzyme's recognition sequence is located.

C. Claim 1 is indefinite over the recitation of "to amplify the tag." It is unclear how sequences of the vector will necessarily still be present at this point in the method, following the instructed restriction digestions. As the points at which restriction digestion are indefinite, it is not possible to assume that vector sequences characteristic to only **some** permutations of possible restriction digestions, would necessarily be always present. Applicant should amend the claims to clarify the oligonucleotides to be used in tag amplification and the known nucleotide regions.

Response to Arguments:

Applicants assert that the rejection of claims 1-3 under 35 U.S.C. 112, second paragraph has been obviated by amendment, however indefiniteness still exists and has been pointed out in the above rejections of the claims as amended.

Claim Rejections - 35 USC § 103

Applicant should note that in light of the standing and new indefiniteness rejections under 112 2nd paragraph, the art rejection is maintained because of the lack of clarity in the claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kinzler et al. in view of Okubo et al. (DNA Sequence, 1991).

Kinzler et al. teach a method for analyzing expression frequencies of genes, which comprises the following steps:

(a) a step of forming a vector primer to which each mRNA derived from a cell of which expression frequencies of genes is to be analyzed, and synthesizing the cDNA, said vector primer comprising a capture system to isolate the defined 3' nucleotide sequence tag when the oligo dT primer for biosynthesis is present(US5,695,937 Col. 5 and Col.6 lines 43-57), along with a recognition sequence for a first restriction enzyme in an inner position from the poly(T)

sequence(See FIG.1A and Col.5 lines 4-25), a recognition sequence for a second restriction enzyme near the other end, and a recognition sequence for a type IIS restriction enzyme in an inner position from the recognition sequence for the second restriction enzyme(See FIG. 1A and Col. 5 lines 12-27 and lines 50-60). The reference is generally teaching the purposeful step of focusing only on the 3' sequences(via combination of capture mechanism and selective restriction digestion) of any gene to maximally identify genes through matching ESTs.

(b) a step of digesting the vector primer to which the cDNA is ligated, with the second restriction enzyme and a third restriction enzyme that does not digest the vector primer as the reference teaches that the invention is not limited to the use of a single first restriction endonuclease or second as "it may be desirable to perform the method of the invention sequentially, using different enzymes to identify a complete pattern of transcription(Col. 5 lines 12-27). The reference further teaches cleaving with restriction enzymes to create compatible, "same shape" ends and "procedures for cloning the defined nucleotide sequence tags of the invention is insertion of the tags into vectors such as plasmids or phage"(Col.7, lines 5-43).

(c) a step of digesting the cyclized vector primer with the first restriction enzyme and the type IIS restriction enzyme to excise a downstream region of the cDNA so that a tag consisting of a part of the cDNA is left, and cyclizing the vector primer again is taught in the reference's Example 1, as they teach that following restriction digestion, the "ditag products were cleaved with NlaIII and...were cloned into the SphI site of pSL301"(Col. 9, lines 10-60).

(d) a step of performing polymerase chain reaction (PCR) by using the vector primer as a template and oligonucleotides having nucleotide sequences corresponding to respective flanking regions of the both sides of the tag contained in the vector primer as primers to amplify the tag,

was taught in the reference as "the ditag can be amplified by utilizing primers which specifically hybridize...and using the standard polymerase chain reaction(PCR) or alternatively by cloning in prokaryotic-compatible vectors"(Col.6, lines 36-57). The reference goes on to teach that "primers are selected to be substantially complementary to the different strands of each specific sequence to be amplified, and that the primers must be sufficiently long to prime the synthesis of extension products in the presence of the agent for polymerization.

(e) a step of ligating the amplification products to form a concatemer of the tags as the reference teaches "preferably, the ditags or concatemers thereof are ligated into a vector for sequencing purposes"(Col.7 lines 23-43).

(f) a step of determining the nucleotide sequence of the concatemer and investigating types and frequencies of tags occurring in the nucleotide sequence.(Col.7 lines 23-43) The reference is generally teaching the concept that through sequencing only a few nucleotide bases for each template it is possible to index the expressed gene in a much smaller scale and thereby affording the ability to identify differentially expressed genes genome wide.

The reference further teaches the above method wherein the ligation reaction in the step (e) is performed in the presence of an adaptor having one end of the same shape as an end of the tag to arrange the adaptor at each end of the concatemer, and the concatemer is amplified by performing PCR using oligonucleotide having a sequence corresponding to the sequence of the adaptor as a primer(See FIG.1A and FIG.1B).

Kinzler et al. does not teach in step (a) a vector primer comprising a linear plasmid vector having a single-stranded poly(T) sequence at one 3' end a recognition sequence for a second restriction enzyme near the other end, and a recognition sequence for a second restriction

enzyme near the other end, and a recognition sequence for a type IIS restriction enzyme in an inner position from the recognition sequence for the second restriction enzyme, nor does the reference teach a step of digesting the vector primer to which the cDNA is ligated, with the second restriction enzyme and a third restriction enzyme that does not digest the vector primer and forms a digested end of the same shape as a digested end obtained with the second restriction enzyme, to excise an upstream region of the cDNA, and cyclizing the vector primer.

However, Okubo et al teach step (a) a vector primer comprising a linear plasmid vector having a single-stranded poly(T) sequence at one 3' end a recognition sequence for a second restriction enzyme near the other end, and a recognition sequence for a second restriction enzyme near the other end, and a recognition sequence for a type IIS restriction enzyme in an inner position from the recognition sequence for the second restriction enzyme, and also Okubo et al. teaches a step of digesting the vector primer to which the cDNA is ligated, with the second restriction enzyme and a third restriction enzyme that does not digest the vector primer and forms a digested end of the same shape as a digested end obtained with the second restriction enzyme, to excise an upstream region of the cDNA, and cyclizing the vector primer(Pg. 138 figures a-d). Okubo et al. teach a method for constructing a library containing the 3' end fragment of cDNA for large scale sequencing of cDNA clones. The reference teaches using a T-tailed vector primer for first strand synthesis, "because it is the most efficient way to prepare the cDNA molecule for directional cloning"(Pg. 137). Okubo teach that the vector plasmid was pUC19 that has the M13 sequence flanking the cloning site. The presence of this flanking sequence, is taught by the reference to allow for common primers to be used for PCR amplification of insert cDNAs as well as for their subsequent sequencing. The reference further

teaches the second strand synthesis to be initiated by nick translation and the resulting molecule to be digested with *MboI* and *BamHI*. *MboI* is used as it will cut within a few hundred bases away from the poly A tail. The reference continues to teach that *BamHI*, whose recognition sequence includes that of *MboI*, makes cohesive termini at the other end of the vector DNA, and therefore, the resulting cleavage products could be circularized in a diluted condition with *E. coli* ligase which cannot ligate unreacted vector primers or undigested molecules(Pgs 137 and 138).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the first principle of the Kinzler method, creating a short nucleotide sequence tag and anchoring it to a streptavidin bead so as to have instead included a method wherein the 3'end fragments of genes are instead anchored to a vector by way of the vector primer methodology taught by Okubo et al. since the method of Okubo provided a "high efficiency that was considered to have been due to the simplicity of the protocol"(Pg 138). Kinzler et al. in its entirety teaches a method "consisting of the same three major principles that define the present application: First, a short nucleotide sequence tag (ex. 9 to 10bp) contains sufficient information content to uniquely identify a transcript provided it is isolated from a defined position within the transcript. Second, random dimerization of tags allows a procedure for reducing bias (caused by amplification and or cloning). Third, concatenation of these short sequence tags allows the efficient analysis of transcripts in a serial manner by sequencing multiple tags within a single vector or clone"(Col.3 lines 25-50). The reference also teaches "all of these principles may be applied independently, in combination, or in combination with other known methods of sequence identification"(Col.3 lines 25-50). To put it even more simply, the reference teaches a method in which very short (9-14 bp) cDNA tags are generated by restriction

digestion, amplified by PCR and ligated, after which the resulting concatemers are sequenced. The tags of the reference and present invention are long enough to identify the corresponding genes unequivocally and the frequency of the tags is a measure of their expression level. As a result, since the method of Okubo presents just another way of capturing the 3' end of a gene whose "high efficiency was considered to have been due to the simplicity of the protocol"(Pg 138); in comparison to the method taught by Kinzler, combining the teachings of Kinzler et al. in view of Okubo et al. would have been obvious at the time the invention was made.

Response to Arguments:

Applicant traversed the rejection on the grounds that the SAGE method possesses many drawbacks, which include:

1). The techniques required for the method are complicated and they can be performed only by specially trained persons;

2). About 1μg of mRNA is required for the measurement, and therefore it is substantially impossible to perform the measurement with a sample that can be obtained in a small amount, for example, a clinical biopsy material, and it is similarly impossible to measure difference of genetic expression in micro tissue portions; and

3). The method theoretically causes considerable measurement errors because a ditag is measured.

Applicant asserts that as a result, the Kinzler et al. reference teaches away from their present invention. In response, applicant is reminded that while certain improvements may be conferred through the practice of the method, the claims define the patented subject matter and as such these improvements are not included as limitations in the claims, or the claims do not clearly

present the limitations that applicant asserts makes novel the present method of gene expression. Applicant must amend their claims to first, make clear the exact embodiment of their method that is operable in their attempt to detect gene expression and second amend the claims to recite the exact limitations they feel represent a contribution over the prior art. As presently claimed, the indefiniteness and broadly claimed method is still seen as being obvious over the teachings of Kinzler et al. in view of Okubo et al.

THE FOLLOWING IS A NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS AMENDMENT TO THE CLAIMS:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte*

Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

Nature of the invention. Claims 1-20 are broadly drawn to a method for analyzing expression frequencies of genes comprising steps of annealing and digesting until the desired vector is established. The specification does not at all enable the ability of this method for analyzing gene expression solely by following the outlined steps found in the same. Applicant should note that limitations exemplified in the specification cannot be read into the claims and as a result the claims are inoperable as presently written. Furthermore, the invention is an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Scope of the invention. The scope of the invention is very broad, claiming a method for analyzing expression frequencies of genes comprising various, broadly claimed steps involving digestion with various restriction enzymes in order to obtain a desired vector which will be used in the execution of the claimed method. Much unpredictability exists in the broad claiming of applicant's steps involved in the formation of their desired vector primer. Specifically, the broad directions for digesting the vector with restriction enzymes I, II, and III(type IIs), include inoperable embodiments as currently claimed. For example if, as instructed in claim 1, the digestion of the vector primer is carried out as broadly as it is claimed, it is possible to obtain a vector primer lacking any cDNA insert, and thus making the invention inoperable. Furthermore, in light of the indefiniteness rejections, it is not only highly unpredictable to practice this invention, but impossible if certain selections that fall within the scope of the invention as claimed are made in the formation of the vector primer..

State of the art. The prior art discloses methods that give explicit instructions for the execution of their methods involving the detection of gene expression. As can be seen from the combination of references above, Kinzler in view of Okubo, disclose specific steps involving guidance in digestion with specific enzymes to specific sites in order to provide an operable method of gene expression detection. However, the present application's method as broadly claimed includes inoperable embodiments and at best is highly unpredictable.

Number of working examples and Guidance provided by applicant. The instant specification only provides guidance and working examples concerning certain embodiments of the invention as claimed. The examples provided in the specification, and those examples in Figures 1-5, serve only as applicant's interpretation of the claims as written. The examples include operable embodiments of the claims as written but do not exemplify the broadly claimed method. Only one interpretation of the restriction enzyme's site placements is reflected in the examples and figures in the specification, all embodiments have not been considered as the broadly claimed method proves to be inoperable as a result of certain enzyme site location selections. Considering the unpredictability surrounding the ability to select the informative restriction enzyme sites as instructed by the claims, as pointed out in the Nature of the invention section of this rejection, the skilled artisan would have to practice undue and unpredictable trial and error experimentation in order to practice the invention with a properly formed vector primer from which gene expression data will be extracted. In addition, considering the lack of working examples showing all possible restriction enzyme site locales even more unpredictability exists in practicing this method.

Level of skill in the art. The level of skill involved in following the directions of the claims as nebulously written to obtain an operable invention is very high, if not impossible.

Unpredictability of the art. There are examples of methods in which the proper guidance is given to allow for the predictable execution of gene expression detection methods as seen in the art rejection above. The present application's disclosure as it is broadly claimed includes much unpredictability if not inoperable based upon its lack of guidance in the claims. In light of these deficiencies, the skilled artisan would be forced to practice undue and unpredictable trial and error experimentation when practicing the instant invention.

Considering the Nature of the invention, the guidance provided by both the prior art and the instant specification, and the broad scope of the invention, it is clear that the skilled artisan would be required to practice undue and unpredictable trial and error experimentation to practice the invention that is claimed.

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Friday from 7:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the Primary examiner in charge of prosecution, Jeffrey Fredman can be reached at (703)308-6568 and if neither examiners can be reached, their supervisor, Gary Benzion, can be reached at (703)308-1152. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703)605-1237.

Sally Sakelaris

9/23/2003

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600